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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,333	GLAZER, PETER M.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-12 and 15-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-12 and 15-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/5/02*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II, claims 7-12 and 15-25 in the reply filed on July 12, 2004 is acknowledged.

Claims 7-12 and 15-25 are pending. Claims 1-6, 13 and 14 have been cancelled.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-12 and 15-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for targeted recombination of a target nucleic acid molecule in vitro or ex vivo wherein the methods comprise contacting a target nucleic acid molecule or an isolated cell with a triple helix forming oligonucleotide (TFO) and a donor oligonucleotide that is complementary to a target nucleic acid sequence, forming a triple helix by hybridizing the TFO to the target nucleic acid, and recombining the donor oligonucleotide into the target nucleic acid to thereby accomplish targeted recombination of the target nucleic acid, wherein the TFO has a Kd of less than 2×10^{-7}, does not reasonably provide enablement for method of in vivo targeted recombination or methods of targeted recombination in which a TFO is utilized which has a Kd of more than 2×10^{-7}. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn to methods of targeted recombination wherein the methods comprise providing a triple-helix forming oligonucleotide (TFO) to a target double-stranded molecule and a donor nucleic acid. The TFO has the property of having a Kd of 2×10^{-6} or less with the target nucleic acid. The donor nucleic acid may be tethered or unlinked to the TFO and recombines into the target nucleic acid sequence. The claims as written are inclusive of methods which are performed in vitro and methods which are performed in vivo (see page 3 of the specification). In particular, claim 10 allows for the use of the targeted recombination to alter the activity of a protein encoded by the target double-stranded nucleic acid. Claims 15-24 are inclusive of methods in which recombination produces a heritable change in the genome of an intact human or animal. While the specification has enabled methods for in vitro and ex vivo targeted recombination using a donor nucleic acid tethered or unlinked to a TFO having a Kd of 2×10^{-7}, the specification has not enabled methods for in vivo targeted mutagenesis or methods in which the TFO has a Kd above 2×10^{-7} for the following reasons:

The specification exemplifies the in vitro treatment of cells and cell extracts with triple-helix forming oligonucleotides and teaches that oligonucleotides having a Kd of 2×10^{-8} or less are capable of inducing mutations in vitro at a rate of 0.2-0.8% (see Example 1 in the specification). An oligonucleotide having a Kd of 3×10^{-5} (AG10) induced mutations at a frequency of .07 as compared to the frequency of .03 induced by an oligonucleotide that did not show significant binding. The specification also teaches that HeLa cell-free extracts treated with the AG30 TFO tethered to or unlinked to a SupFg1 donor fragment had a recombination frequency of 45×10^{-5} and 40×10^{-5} , respectively.

However, the specification does not teach one of skill in the art how to use TFOs having a Kd of more than 2×10^{-7} for the purposes of achieving targeted recombination or targeted mutagenesis. As set forth on page 5 of the specification, the TFO must bind with the target nucleic acid with sufficient specificity and stability to allow for targeted recombination to occur. There is no showing in the specification that TFOs having Kd's in the range of 2×10^{-6} bind to target nucleic acids sufficiently to 'achieve significant intracellular interactions.' The specification does not exemplify the effective use of any TFOs having a Kd in the range of 2×10^{-6} in combination with a tethered or untethered donor fragment. The ability of a TFO to bind to a target nucleic acid and to stimulate recombination and repair is highly unpredictable. In view of this unpredictability and the lack of specific guidance in the specification as to how to use TFOs having Kd's that do not allow for specific and significant binding to target nucleic acids, undue

experimentation would be required for one of skill in the art to practice the claimed method using TFOs having a Kd higher than 2×10^{-7}.

Secondly, the specification has not enabled methods for targeted recombination in vivo or methods in which targeted recombination produces heritable changes in the genome of an intact animal or human. The specification does not exemplify the in vivo use of TFOs/donor fragments, particularly the in vivo use of these oligonucleotides for the purposes of targeted mutagenesis. The activity of triple-helix forming oligonucleotides in vivo is unpredictable in the absence of in vivo data because the success of the therapy is dependent on adequate concentrations of the oligonucleotide reaching the desired site in vivo, hybridizing the TFO to a specific gene sequence, and recombining the donor fragment into the target gene sequence. Specifically, in vivo oligonucleotide therapies are unpredictable for the following reasons: (I) The triple-helix forming oligonucleotide may be degraded in blood and tissues under physiological conditions and therefore may not reach the target site; (ii) The ability of the oligonucleotide to be taken up by the cell is expected to be different under physiological conditions as versus tissue culture, i.e. the permeability of the cell would be different under physiological conditions and would be expected to vary with cell type; (iii) It is not clear what would be the optimum concentration of the oligonucleotide required for effective treatment, the mode of administration and the pharmacokinetics of therapy; (4) The ability of the oligonucleotide to form a triple helix under physiological conditions is unpredictable since the formation of the triple-helix varies significantly with oligonucleotide length, and chemical composition and is highly affected by the presence

of secondary and tertiary nucleic acid structures; and (5) the ability of the donor oligonucleotide to bind to and recombine with the target nucleic acid varies significantly with the length and chemical composition of the donor oligonucleotide and the recombination process is also affected by secondary and tertiary nucleic acid structures. Therefore, for each therapeutic oligonucleotide, one must develop de novo the appropriate set of parameters for in vivo function. While the specification provides a general discussion regarding the administration of TFOs in combination with donor oligonucleotides, there is insufficient guidance provided in the specification as to how to use any particular oligonucleotides for therapeutic purposes in vivo and therefore one is left to develop de novo the appropriate techniques for selection, delivery and effective use of each therapeutic oligonucleotide. In view of the unpredictability in the art of oligonucleotide therapeutics, the skilled artisan would not accept that results obtained in vitro are reasonably predictive of the results obtained in vivo for because the correlation between in vitro and in vivo results is not a general characteristic that can be applied to each and every pharmaceutical composition and the record has not established a universal correlation between the results obtained in vitro with triple-helix forming oligonucleotides and the results obtained in vivo. Moreover, for triple-helix forming oligonucleotides which induce mutagenesis, the ability to use such oligonucleotides in vivo is further unpredictable because there is no means to predict a priori where a mutation or what particular mutation will occur.

Further, Wang (page 804; Science. 1996. 271: 802-805; cited in the IDS) teaches that the triple-helix forming oligonucleotides induce a scattered spectrum of

mutations, rather than specific mutations. As discussed in the specification, targeted mutagenesis is performed to achieve the result of activating, inactivating or altering the activity and function of a gene. However, the process of targeted mutagenesis with triple-helix forming oligonucleotides does not result in a single, specific mutation. Rather, this process, as exemplified in the specification, results in the formation of an array of point mutations and deletions at or surrounding the region to which the oligonucleotide binds. While the donor oligonucleotide may be used to introduce a specific sequence into the target nucleic acid, the binding of the TFO also introduces an array of nonspecific mutations at the target site or adjacent thereto. For therapeutic purposes, the induction of random mutations would not provide an art recognized acceptable means for the treatment of a disease because there is no predictable means for determining which mutations would have a null effect and which mutations may actually result in the inappropriate stimulation or inhibition of gene expression.

It is also highly unpredictable as to whether the TFO/donor oligonucleotide would be capable of inducing a sufficient amount of recombination and mutations in a sufficient quantity of cells to impart a therapeutic effect in view of the fact that the specification teaches that even in vitro such TFOs tethered to a donor fragment induce recombination at a frequency of 45×10^{-5} and TFOs not linked to the donor fragment induce recombination at a frequency of 40×10^{-5}. Moreover, in view of the cellular mechanisms for repairing mutations, it is highly unpredictable as to whether a sufficient number of cells would maintain the mutation and pass the mutation on to secondary cells in order to allow for an effective therapy.

With respect to the recitation in claims 15-24, the specification has not enabled methods in which targeted recombination produces heritable changes in the genome of an intact human or animal. The specification teaches that in mice treated with AG30 (no donor fragment provided), mutagenesis was observed in liver, skin, kidney, colon, small intestine and lung cells at a frequency five fold that of background (see Example 7). However, the specification does not teach the frequency at which recombination or mutagenesis is achieved in germline cells in methods which use a TFO alone or in combination with a donor fragment. Given the low frequency at which recombination and mutagenesis occurs in vitro, let alone in vivo, it is highly unpredictable as to whether a sufficient number of germline cells can be altered by recombination so as to allow for the inheritance of a genomic change in the offspring an animal treated with a TFO/donor fragment.

At the time the invention was made, it is well recognized in the art that significant experimentation would required to practice the in vivo administration of triple helix forming oligonucleotides. For example, Wang (Molecular and Cellular Biology, 1995, p. 1767; cited in the IDS) states that "(c)learly, forming a triple helix in vitro under controlled buffer conditions is an easier task than doing so in vivo with exogenously added oligonucleotides, which must be taken up by the cells, enter the nuclei, and bind to the target site under suboptimal conditions". Wang (p. 1767) goes on to state that "(t)heoretically, targeted mutagenesis and inactivation of selected genes might also eventually have therapeutic applications. However, the general applicability of this approach will depend on the extension of the third-strand binding code and the

development of nucleotide analogs so that triple helix formation is not limited to polypurine sequences." Yet, there is no specific guidance provided in the specification as to how to overcome the numerous known and unknown obstacles associated with in vivo targeted recombination and mutagenesis with TFOs and donor oligonucleotides, and as evidenced by Wang, excessive experimentation would be required to accomplish the successful in vivo application TFO/donor oligonucleotides that are capable of targeting specific sequences in vivo.

The teachings of Chan (Journal of Biological Chemistry. 1999. 274: 11541-11548; cited in the IDS) also emphasize the fact that additional research is required before TFOs tethered to donor oligonucleotides can be used in vivo. In particular, Chan concludes that "The TD-TFO approach as a method for DNA sequence modification has the potential to be useful a research tool and may eventually provide the basis of a gene therapy strategy."

Barre (PNAS (2000) 97:3084-3088; see abstract) emphasis the requirement for mutagenesis to occur at a sufficient frequency in order for TFOs to be effective in vitro or in vivo. Barre (page 3088) states that "If this value is taken to represent the expected maximal frequency of mutations on an endogenous target, the proportion of targets reached by the TFO thus can be estimated as one in a thousand – a proportion too low to envision any therapeutic applications."

The unpredictability in the art of using TFOs in vivo is further highlighted by Seidman et al (The Journal of Clinical Investigation. August 2003, 112: 487-494). This

reference (which is co-authored by the present inventor) teaches that "Biological applications of TFOs are compromised by fundamental considerations, as well as limitations imposed by physiological conditions....triplex formation involves conformational changes on the part of the third strand, and some distortion of the underlying duplex. Pyrimidine motif triplexes are unstable at physiological pH because of the requirement for cytosine protonation that occurs at relatively acidic pH (pKa = 4.5)...All of these factors impose kinetic barriers on triplex formation and reduce the stability of triplexes once formed" (pages 487-488). With respect to the importance of the stability of binding, Seidman (page 488) teaches "TFOs with equilibrium dissociation constants of approximately 10^{-9} M were active; those with Kd's of 10^{-6} M were not." The reference concludes that "It seems likely that recent advances in oligonucleotide chemistry have considerable potential for the development of TFOs with robust gene targeting activity. This will require coordinated effort between chemists and biologists, but recent data suggests that this effort will be rewarded." Accordingly, the teachings of this reference indicate that even as of 2003, additional research is required before TFO/donor oligonucleotides can be used for in vivo applications.

In summary, there is insufficient guidance provided in the specification as to how to use the claimed TFOs/donor oligonucleotides for in vivo applications. The specification as filed provides only general guidelines for the administration of TFOs and donor oligonucleotides, leaving one to develop de novo the appropriate techniques for in vivo delivery and effective use of the broadly claimed methods. Accordingly, in view of the breadth of the claims, the recognized unpredictability in the art of targeted

recombination and mutagenesis and in the art of the in vivo administration of TFO/donor oligonucleotides, and in view of the lack of working examples in the specification, it would require undue experimentation for one of skill in the art to practice the invention as broadly claimed.

3. Claims 7-12 and 15-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 7-12 and 15-25 are indefinite. The claims are drawn to a method for targeted recombination of a nucleic acid molecule. However, the claims recite only the steps of providing a single stranded oligonucleotide and a donor nucleic acid. The claims do not clarify how the steps of providing these molecules result in targeted recombination. Therefore, it is unclear as to whether the method is one for targeted recombination or one for providing a single stranded oligonucleotide and a donor nucleic acid.

B. Claims 9, 12 and 25 are indefinite over the recitation of "the donor DNA fragment" because this phrase lacks proper antecedent basis. While the claims previously refer to a donor nucleic acid, the claims do not previously refer to a donor DNA fragment.

C. Claims 15-24 are indefinite and confusing over the recitation of "to produce heritable changes in the genome of an intact human or animal" because it is not clear as to how this phrase is intended to further limit the claimed method. For example, it is unclear as whether claims 15-24 are intended to be limited to methods in which targeted recombination is performed in an intact human or animal or if the claims are intended to

be limited to methods in which targeted recombination is performed in a cell or cell extract and the resulting recombined target nucleic acid could potentially be used in some unstated manner to produce a heritable change. It is unclear as to whether "heritable change" refers to inheritance of a change in the genome into any somatic daughter cell or whether this phrase is intended to refer to genomic changes that are inherited by human or animal offspring. It is also unclear as to whether the "target region of the genome" is considered to be the same as or different from the "target sequence." Further, the claims recite a step of "injecting an oligonucleotide" but do not clarify what the oligonucleotide is injected into. Additionally, it is unclear as to whether the oliogonucleotide recited in claims 15-24 is the same as or different from the single stranded oligonucleotide recited in claim 7, from which claims 15-24 depend. The claims do not clearly set forth the relationship between the single stranded oligonucleotide recited in claim 7 and the injected oligonucleotide of claims 15-24.

D. Claim 19 is indefinite. The claim recites the use of an exogenously supplied DNA fragment. However, it is unclear as to whether the exogenously supplied DNA fragment is the same as or different from the donor nucleic acid. In the later case, it is unclear as to how both the exogenously supplied DNA fragment and the donor nucleic acid are utilized in the method of targeted recombination. Similarly, claim 20 is indefinite over the recitation of "a tethered DNA fragment" because it is unclear as to what is intended to be the relationship between the tethered DNA fragment, the exogenously supplied DNA fragment and the donor nucleic acid and it is unclear as to how this claim is intended to further limit the claimed method.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 7-8, 10-12, 15-21, 23-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 5,776, 744. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '744 are both inclusive of methods for effecting targeted recombination wherein the methods comprise introducing into a cell a TFO and a donor nucleic acid, allowing the TFO to form a triple helix with a target nucleic acid and inducing recombination between the target nucleic acid and the donor nucleic acid. The claims of '744 and the present claims further include the use of donor nucleic acids that are at least 40 basis in length and the use of TFOs that have a Kd of 2×10^{-7}, and having a length of 7 to 50 nucleotides or 10 to 30 nucleotides. The claims of '744 and the present claims also allow for methods in which the target nucleic acid contains a mutation and the mutation is corrected by homologous recombination.

5. Claims 9, 22 and 25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 5,776,744 in view of Chan.

The present claims and the claims of ‘744 are both inclusive of methods for effecting targeted recombination wherein the methods comprise introducing into a cell a TFO and a donor nucleic acid, allowing the TFO to form a triple helix with a target nucleic acid and inducing recombination between the target nucleic acid and the donor nucleic acid. The claims of ‘744 and the present claims further include the use of donor nucleic acids that are at least 40 basis in length and the use of TFOs that have a Kd of 2×10^{-7}, and having a length of 7 to 50 nucleotides or 10 to 30 nucleotides. The claims of ‘744 and the present claims also allow for methods in which the target nucleic acid contains a mutation and the mutation is corrected by homologous recombination.

Present claims 9 and 25 differ from the claims of ‘744 in that the claims of ‘744 do not require that the use of a donor nucleic acid tethered to the TFO. However, Chan et al (see, for example, page 11542) teach a method of targeted recombination wherein the methods comprise contacting a cell with a single stranded TFO tethered to a donor oligonucleotide under conditions in which the TFO forms a triple helix with a target nucleic acid and the donor oligonucleotide recombines into the target nucleic acid. With respect to using TFOs tethered to the donor fragment, Chan (page 11543) states “This arrangement facilitates target site recognition via triplex formation while positioning the donor fragment for possible recombination and information transfer. This strategy also attempts to exploit the ability of the triple helix itself to provoke DNA repair at the binding

site, potentially increasing the probability of recombination of the tethered donor DNA." In view of the teachings of Chan, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have performed the recombination method of '744 by using a TFO tethered to a donor nucleic acid because Chan teaches that using TFOs tethered to the donor nucleic acid provides an effective means for introducing the TFOs and donor nucleic acids into target cells.

With respect to claim 22, the claims of '744 do not specifically require targeting xeroderma pigmentosum gene. However, Chan teaches that TFOs/donor fragments can be used to introduce or correct a mutation in a targeted nucleic acid (see, for example, page 11542). Chan (page 11546) also teaches that patients with Xeroderma pigmentosum are deficient in the nucleotide excision recognition factor XPA due to mutations in XPA and that TFO stimulated recombination depends on XPA activity. In view of the teachings of Chan, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the TFO/donor recombination method to the XPA gene in order to generate mutations in this gene which would allow researchers to study how mutations in XPA effect nucleotide excision repair and TFO-stimulated recombination/repair processes.

Priority

6. The present claims are entitled to priority only to the instant filing date of October 15, 2001. It is noted that parent application 09/411,291 does not provide basis for the concepts in the present claims of performing methods of targeted recombination

using a TFO in combination with a tethered or unlinked donor nucleic acid; the use of a TFO having a Kd of "2×10^{-6} or less"; the application of the recombination method to produce "heritable changes in the genome of an intact human or animal."

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7-12, 15-21, 23-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Chan et al (Journal of Biological Chemistry. 1999. 274: 11541-11548; cited in the IDS).

Chan et al (see, for example, page 11542) teach a method of targeted recombination wherein the methods comprise contacting a cell with a single stranded TFO tethered or unlinked to a donor oligonucleotide under conditions in which the TFO forms a triple helix with a target nucleic acid and the donor oligonucleotide recombines into the target nucleic acid. In particular, Chan teaches that the combination of TFOs and donor oligonucleotides were able to mediate gene conversion or correction in the supF reporter gene (see page 11545). In particular, Chan teaches that the TFO (AG30) is single stranded, 30 nucleotides in length and comprises polypurine and polypyrimidine nucleotides (see page 11543 and Figure 2). AG30 has a Kd of 3×10^{-8} and the TFO tethered to the donor nucleic acid (A-AG30) has a Kd of 5×10^{-8} (see page

11543). With respect to claims 12 and 25, Chan teaches that the donor nucleic acid is 40 or 44 nucleotides in length (see page 11543). With respect to claims 15-21 and 23-24, the method of Chan is one in which the introduced genomic change could be used to pass the genomic change onto daughter cells in an animal. With respect to claim 17, Chan teaches transfection of oligonucleotides into cells using LipofectAmine and teaches in vitro triplex formation in a binding buffer, and thereby is considered to teach providing the TFO in a physiologically acceptable carrier. Accordingly, the method of Chan is considered to anticipate the claimed method of targeted recombination.

Claim Rejections - 35 USC § 103

8 . The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chan et al (Journal of Biological Chemistry. 1999. 274: 11541-11548).

The teachings of Chan are presented above. Chan does not specifically exemplify methods in which targeted recombination is performed using a xeroderma pigmentosum gene. However, Chan teaches that in combination donors and TFOs can be used to introduce or correct a mutation in a targeted nucleic acid (see, for example, page 11542). Chan (page 11546) also teaches that patients with Xeroderma pigmentosum are deficient in the nucleotide excision recognition factor XPA due to mutations in XPA and that TFO stimulated recombination depends on XPA activity.

In view of the teachings of Chan, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the TFO/donor recombination method to the XPA gene in order to generate mutations in this gene which would allow researchers to study how mutations in XPA effect nucleotide excision repair and TFO-stimulated recombination/repair processes.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)-272-0782.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Carla Myers

September 20, 2004

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER